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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ERIC J. BENJAMIN,
REINHARDT B. BAUDY, and MICHAEL R. BRANDT

Appeal 2009-008378[1]
Application 10/820,215
Technology Center 1600

Decided: February 23, 2010

Before TONI R. SCHEINER, DONALD E. ADAMS, and
LORA M. GREEN, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-56. We have jurisdiction under 35 U.S.C. § 6(b).

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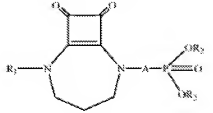
[1] Oral Hearing held February 2, 2010.

STATEMENT OF THE CASE

Claims 1, 10, and 13 are representative of the claims on appeal, and read as follows:

1. A pharmaceutical composition for intranasal administration comprising:

a) a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R_1 is hydrogen;

A is $-(CH_2)_n-$, where n is 2;and

R_2 and R_3 are hydrogen; and

b) one or more pharmaceutically acceptable additives for forming a composition for intranasal administration.

10. A method for treating at least one condition in a mammal selected from a cerebral vascular disorder selected from cerebral ischemia, cerebral infarction or cerebral vasospasm; cerebral trauma; muscular spasm; a convulsive disorder selected from epilepsy or status epilepticus; hypoglycemia; cardiac arrest; asphyxia anoxia; or spinal chord injury comprising administering intranasally to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

13. A method for treating at least one condition in a mammal selected from anxiety disorders; mood disorders; schizophrenia; schizophreniform disorder; or schizoaffective disorder comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

The Examiner relies on the following evidence:

Lin	EP 0778023 A1	Apr. 12, 1996
Wilk	US 7,345,032 B2	Mar. 18, 2008
Benjamin	US 2005/0142192 A1	Jun. 30, 2005
Brandt	US 7,098,200 B2	Aug. 29, 2006

Appellants rely on the following evidence:

Wood, *The NMDA receptor complex: A long and winding road to therapeutics*, 8 IDrugs 229-234 (2005).

Heresco-Levy, *Glutamatergic neutrotransmission modulators as emerging new drugs for schizophrenia*, 10 Expert Opin Emerg Drugs, 827-844 (2005).

Bergink et al, *Glutamate and anxiety*, 14 European Neuropsychopharmacology 175-183 (2004).

Parsons, *NMDA receptors as targets for drug action in neuropathic pain,* 429 European Journal Pharmacology 71-78 (2001).

Brown, *N-Methyl-D-Aspartate Receptor (NMDA) Antagonists as Potential Pain Therapeutics*, 6 Current Topics in Medicinal Chemistry 749-770 (2006).

McCulloch, *Excitatory amino acid antagonists and their potential for the treatment of ischaemic brain damage in man*, 34 Br. J. Clin Pharmacology 106-114 (1992).

Trujillo, *Are NMDA receptors involved in opiate-induced neural and behavioral plasticity? A review of preclinical studies*, 151 Psychopharmacology 121-41 (2000) (Abstract only).

The following grounds of rejection are before us for review:

I. Claims 1-56 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

II. Claims 1-26 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Lin.

III. Claims 1-9 and 26 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 26-29 of copending Application No. 10/969,715, now U.S. Patent 7,345,032.

IV. Claims 27-56 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-95 and 104-108 of copending Application No. 10/961,871, U.S. Pub. No. 2005/0142,192.

V. Claims 21-24 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 7,098,200.

We affirm all of the rejections of record.[2]

ISSUE (Enablement)

The Examiner concludes that the claims are not enabled.

Appellants contend that the claims are enabled, as they have shown that there is a nexus between NMDA antagonists and the treatment of the diseases and/or disorders listed in the claims to support enablement of claims 1 to 56.

Thus, the issue on Appeal is: Have Appellants demonstrated that the Examiner erred in concluding that the claims are not enabled?

[2] As Appellants do not argue the merits of rejections III, IV, and V (Reply Br. 11), we summarily affirm those rejections.

FINDINGS OF FACT

FF1 According to the Specification:

> The present invention relates to intranasal compositions for administering [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)alkyl]phosphonic acid and derivatives thereof, and methods of use thereof.

(Spec. 1.)

FF2 The Specification teaches that the compounds are NMDA antagonists, and have improved bioavailability when administered intranasally. (*Id.* at 2.)

FF3 The Specification teaches that "[s]ubstantial preclinical and clinical evidence indicates that inhibitors of the N-methyl-D-aspartate (NMDA) receptor have therapeutic potential for treating numerous disorders." (*Id.*)

FF4 Specifically, the Specification teaches:

> [T]he present invention provides methods for treating conditions associated with glutamate abnormalities that includes administering intranasally to a mammal in need thereof a therapeutically effective amount of at least one compound of formula (I). As used herein, "associated with" refers to conditions directly or indirectly caused by glutamate abnormalities. "Glutamate abnormality" refers to any condition produced by a disease or a disorder in which glutamate, typically in increased amounts, is implicated as a contributing factor to the disease or disorder. Conditions believed to be associated with glutamate abnormality include, but are not limited to, cerebral vascular disorders such as cerebral ischemia (e.g., stroke) or cerebral infarction resulting in a range of conditions such as thromboembolic or hemorrhagic stroke, or cerebral vasospasm; cerebral trauma; muscular spasm; convulsive disorders such as epilepsy or status epilepticus; glaucoma; pain; anxiety disorders such as such as panic attack, agoraphobia, panic disorder, specific phobia, social phobia, obsessive compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized

> anxiety disorder, separation anxiety disorder, or substance-induced anxiety disorder; mood disorders such as bipolar disorders (e.g., bipolar I disorder, bipolar II disorder, and cyclothymic disorder), depressive disorders (e.g., major depressive disorder, dysthymic disorder, or substance-induced mood disorder), mood episodes (e.g., major depressive episode, manic episode, mixed episode, and hypomanic episode); schizophrenia; schizophreniform disorder; schizoaffective disorder; cognitive impairment such as memory loss; and chronic neurodegenerative disorders such as Parkinson's disease, Huntingdon's disease, Alzheimer's disease, amyotrophic lateral sclerosis, or chronic dementia related to, for example, Lewy body disease, Alzheimer's disease, fronto temporal, or AIDS. With respect to the mental disorders listed above such as schizophrenia, mood disorders and anxiety disorders, reference is made to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Washington, DC, American Psychiatric Association (1994) for a more complete description of each of the mental disorder.
>
> Additional conditions believed to be related to glutamate abnormalities include inflammatory diseases; hypoglycemia; diabetic end organ complications; cardiac arrest; asphyxia anoxia, such as from near drowning, pulmonary surgery and cerebral trauma; and spinal chord injury. The compounds of the present invention may also be used to treat fibromyalgia, and complications from herpes zoster (shingles) such as prevention of post-herpetic neuralgia. The compounds useful in the present invention may also be used to prevent tolerance to opiate analgesia or to help control symptoms of withdrawal from addictive drugs. Thus, the present invention provides methods for treating each of the aforementioned conditions that includes administering intranasally to a mammal in need thereof a therapeutically effective amount of at least one compound of formula (I).

(*Id.* at 19-20.)

FF5 The Specification notes:

> The intranasal pharmaceutical composition of the present invention, in addition to containing a therapeutically effective amount of at least one compound of formula (I), contains one or more pharmaceutically acceptable additives for forming a composition for intranasal administration. By "one or more pharmaceutically acceptable additives for forming a composition for intranasal administration" it is meant one or more substances that facilitate delivery of the compound of formula (I) by intranasal administration. Examples of pharmaceutically acceptable additives for forming a composition for intranasal administration include liquid or solid carriers; absorbance enhancers; pH adjusting agents; buffers; metal chelating agents; thickening agents; humectants; or bioadhesives or combinations thereof. Preferably, these additives in total will constitute at least about 0.25 weight percent, more preferably from about 0.25 weight percent to about 95 weight of the composition, based on the total weight of the composition.

(*Id.* at 14.)

FF6 One of the liquid carriers taught by the Specification is water. (*Id.* at 15.)

FF7 The Examiner rejects claims 1-56 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. (Ans.[3] 3.) As Appellants do not argue the claims separately, we focus our analysis on claim 13, and the remaining claims stand or fall with that claim. 37 C.F.R. § 41.37(c)(1)(vii).

FF8 The Examiner finds that the Specification does not enable the full scope of the claimed subject matter. (Ans. 3.)

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[3] All references to the Examiner's Answer (Ans.) are to the Answer dated October 10, 2007.

FF9 The Examiner notes that "[w]hile the treatment of cerebral ischemia has been linked with NMDA the art does not recognize use of such inhibitors as broad based drugs for treating all [the] disorders instantly embraced." (*Id.* at 4.)

FF10 The Examiner further notes that *Brown* (2006), provided by Appellants, "indicates that deleterious side effects observed with many of the compounds in clinical trials have raised the question if this is a mechanism-based effect, which cannot be overcome." (*Id.* at 9.)

FF11 Trujillo, an abstract submitted by Appellants, states that "NMDA receptor antagonists appear to inhibit the neural plasticity underlying some forms of opiate tolerance, sensitization and physical dependence, suggesting that NMDA receptors are involved in the development of these drug-induced changes in behavior."

FF12 Wood, cited by Appellants teaches:

> While there are a number of excitatory amino acid (EAA) receptor subtypes present in the central nervous system (CNS), the *N*-methyl-D-aspartate (NMDA) receptor subtype has received the greatest investment of resources with regard to drug discovery, largely because of its demonstrated roles in a vast array of CNS functions. However, this wide range of CNS functions becomes a complicating issue when developing an NMDA receptor modulator that is both clinically efficient and lacks serious CNS side effects. Accomplishing this has been particularly challenging since significant disruptions of the dynamic balance between EAAs and the inhibitory amino acid neurotransmitter γ-amino butyric acid (GABA) result in a spectrum of CNS side effects that range from mild to serious.

(Wood, 229, paragraph bridging columns 1 and 2 (reference omitted).)

FF13 Wood teaches further that "[i]n preclinical studies of NMDA receptor antagonists, a number of potential clinical limitations were revealed, for example: ataxia and catatonia; sedation; psychotomimetic actions and confusion; hypertension; and cerebral cortical vacuolization involving cytoplasmic vacuoles in limbic cortical, potentially leading to neuronal necrosis." (*Id.* at 230, first column.)

FF14 Wood notes that "NMDA receptor antagonists demonstrated neuroprotective potential against ischemic stroke in preclinical models, but failed in the clinic." (*Id.* at 231, first column.) Wood notes further that "NMDA receptor modulators will probably never be effective treatments for stroke." (*Id.*)

FF15 Bergink, also cited by Appellants, is a review of the role of glutamate in anxiety. (Bergink, Abstract.)

FF16 Bergink teaches that the NMDA receptor has been directed towards the NMDA receptor, but that the utility of NMDA antagonists is "greatly hampered by adverse effects because of interference with receptors throughout the whole CNS and body." (*Id.* at 180, second column.) Thus, Bergink teaches that "[t]his has led to the conclusion that NMDA receptor antagonism is not a valid therapeutic approach for the treatment of anxiety disorders." (*Id.* at paragraph bridging pp. 180-81.)

PRINCIPLES OF LAW

"[E]nablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' That *some* experimentation may be required is not fatal; the issue is whether the amount

of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) (citation omitted). "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."). Tossing out the mere germ of an idea does not constitute enabling disclosure. "While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

> If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis.

Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1325 (Fed. Cir. 2005).

ANALYSIS

Appellants argue that the claims are enabled, as they have shown that "there is a nexus between NMDA antagonists and the treatment of the diseases and/or disorders listed in the claims to support enablement of claims 1 to 56." (App. Br. 11.) Appellants assert further that "the claims are enabled with respect to the prevention of opiate tolerance." (*Id.*) Appellants argue, citing Trujillo, that the Examiner has not presented any evidence that the claimed compounds "would not be useful in preventing opiate tolerance, especially in light of the fact that NMDA receptor antagonists are known to prevent the opiate analgesia tolerance." (App. Br. 11.)

Appellants argue that the composition claims are enabled, as the Specification teaches how to make the compounds, and also how to formulate them into intranasal compositions. (*Id.* at 12). Appellants also argue that the claims are drawn to "methods for treating conditions associated with glutamate abnormalities, *i.e.*, conditions produced by a disease or disorder in which glutamate, typically in increased amounts, is implicated as a contributing factor." (*Id.*) Appellants submit that they have provided a number of references, such as Wood, Brown, and Bergink, "that show that there is a recognized correlation between antagonism at the NMDA receptors and the specified diseases and conditions set forth in the claims." (*Id.* at 13.)

Appellants assert further that the Specification demonstrates that the intranasal compositions of the invention are NMDA receptor antagonists "in the art-recognized *in vivo* prostaglandin E_2-induced thermal hypersensitivity test." (*Id.* at 14.) Appellants assert that the model is recognized as correlating

to a specific condition, it should be accepted as correlating in the absence of evidence to the otherwise. (*Id.*)

We have carefully considered the evidence of record and Appellants' arguments, and conclude that the evidence supports the Examiner's conclusion that the claims are not enabled. For example, representative claim 13 is drawn to the treatment of anxiety. The only experimental data provided by the Specification is the *in vivo* prostaglandin E_2-induced thermal hypersensitivity test. Appellants, however, have not presented any evidence that model is an art-recognized model for anxiety.

In addition, the references provided by Appellants demonstrate that the targeting of the NMDA receptor in the treatment of various disorders has been problematic at best. For example, Wood teaches that because the NMDA receptor is involved in such a wide variety of CNS functions it is difficult to obtain modulation at that receptor that is clinically efficient without having too many serious side effects. (FF12.) As to the treatment of anxiety in particular, Bergink teaches that because the use of NMDA receptors in the treatment of the disorder is hampered by adverse effects due to interference with NMDA receptors in the CNS and throughout the whole body, the use of an NMDA receptor antagonist is not "a valid therapeutic approach for the treatment of anxiety disorders." (FF16.)

Moreover, while Appellants argue that the claims are enabled with respect to opiate tolerance, they do not point to which claim is drawn to a method of preventing opiate tolerance and present separate arguments as to its patentability. In addition, the only evidence they provide in support that the claims are enabled for a method of preventing opiate tolerance is the abstract

of Trujillo, but they do not provide the underlying reference. The abstract talks about opiate tolerance in general, but does not address the claimed class of NMDA antagonists.

CONCLUSION OF LAW

We conclude that Appellants have not demonstrated that the Examiner erred in concluding that the claims are not enabled.

We thus affirm the rejection of claims 1-56 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

ISSUE (Anticipation)

The Examiner finds that the composition of claim 1 is anticipated by Lin.

Appellants contend that Lin cannot anticipate the composition of claim 1 as Lin never discloses a product containing both rapamycin and EAA-090 that is administered intranasally.

Thus, the issue on appeal is: Have Appellants demonstrated that the Examiner erred in finding that Lin anticipates the composition of claim 1?

FINDINGS OF FACT

FF17 The Examiner rejects claims 1-26 under 35 U.S.C. § 102(b) as being anticipated by Lin. (Ans. 5.) As Appellants do not argue the claims separately, we focus our analysis on claim 1, and claims 2-26 stand or fall with that claim.

FF18 The Examiner finds that Lin teaches "the composition and method of use of the [claimed] compounds of formula (1) where A is $-CH_2CH_2-$ and R_1, R_2 and R_3 is H." (*Id.*)

FF19 Specifically, Lin teaches a use for rapamycin and derivatives thereof (Lin, p. 2, ll. 3-4), in combination with an NMDA antagonist, such as [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid (EAA-090) (*id.* at 3, ll. 7-10).

FF20 Lin teaches that rapamycin and NMDA antagonists "can be administered simultaneously or sequentially without regard to the order of administration." (*Id.* at 3, ll. 7-8.)

FF21 Lin teaches further that the "invention provides a pharmaceutical composition comprising rapamycin and a NMDA . . .antagonist and a pharmaceutically acceptable carrier." (*Id.* at 3, ll. 24-25.)

FF22 Lin teaches that the pharmaceutical carrier may be liquid. (*Id.* at 6, l. 57-58.) Liquid carriers taught by Lin include water, an organic solvent or both, and may also contain other pharmaceutically acceptable additives. (*Id.* at 7, ll. 11-19).

FF23 Lin also teaches that rapamycin may be administered nasally. (*Id.* at 6, ll. 25-26.)

PRINCIPLES OF LAW

An anticipatory reference under 35 U.S.C. § 102 "must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the

cited reference." *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972). The reference, however, need not have reduced to practice the subject matter in order to serve as an anticipatory reference. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009).

Disclosure of a method of using any one of a small group of compounds can anticipate later claim to method of using a specific one of them. *See, e.g., Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368 (Fed. Cir. 2005). The claims at issue in that case were directed to a method of topically applying ascorbyl fatty acid ester and the prior art disclosed a cosmetic for topical application that contained any one of fourteen skin benefit ingredients, one of which was ascorbyl palmitate. *Id.* at 1373. The court "reject[ed] the notion that one of these ingredients cannot anticipate because it appears without special emphasis in a longer list. To the contrary, the disclosure is prior art to the extent of its enabling disclosure." *Id.* at 1376. The prior art in Perricone "specifically disclose[d] ascorbyl palmitate. That specific disclosure, even in a list, makes this case different from cases involving disclosure of a broad genus without reference to the potentially anticipating species." *Id.* at 1377.

ANALYSIS

Appellants argue that Lin does not anticipate the composition of claim 1 as Lin "never discloses a product containing both rapamycin and EAA-090 that is administered intranasally." (App. Br. 16) Appellants argue that while Lin discloses intranasal administration of rapamycin, the reference also teaches that the NMDA antagonist does not have to be administered simultaneously with the rapamycin, thus the administration of the NMDA antagonist intranasally is

not inherent in the disclosure of Lin. (*Id.*) According to Appellants, "[t]he fact that intranasal administration of both the rapamycin and EAA-090 might have been carried out is insufficient." (*Id.*)

Appellants' arguments are not convincing, as Appellants are arguing method limitations (administration intranasally) when claim 1 is drawn to a composition. Lin specifically teaches a composition comprising rapamycin, EAA-090 (a compound of formula 1 as set forth in claim 1), and a pharmaceutically acceptable carrier (FF21), which may be a liquid (FF22). Claim 1 merely requires "one or more pharmaceutically acceptable additives for forming a composition for intranasal administration," which the Specification teaches may be a liquid carrier. Appellants have not provided any evidence or argument that the composition of Lin comprising rapamycin, EAA-090, and a liquid carrier, such as water, would not be a composition suitable for intranasal composition.

CONCLUSIONS OF LAW

We find that Appellants have not demonstrated that the Examiner erred in finding that Lin anticipates the composition of claim 1.

We thus affirm the rejection of claim 1 under 35 U.S.C. § 102(b) as being anticipated by Lin. As claims 2-26 stand or fall with claims 1, we affirm the rejection as to claims 2-26 as well.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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